it is possible that dehydrogenation of glycolate occurs much more readily than does the reduction of the intermediates *via* reaction with glycolate. However, since the reaction is conducted in stainless steel equipment, it is likely that the metal surface catalyzes the reaction of hydrogen with the indolenine or indole glycolate. Conditions employing lower reaction temperatures (100–150°) in the presence of added Raney nickel, however, were ineffective in producing indoleacetic acid, although traces detectable by paper chromatography were formed at temperatures as low as 100°.

The fact that 1,2-dimethylindole is unreactive towards potassium glycolate and is recovered unchanged under the present reaction conditions is of interest. With this isomer, an indolenine cannot form and it is attractive to suggest that the reaction must proceed through reduction of this intermediate as opposed to hydrogenolysis of an indoleglycolate. However, the 1-substituent may, more simply, prevent the formation of an indole anion thus precluding the initial condensation of glyoxalate. This inertness does establish in the present case and in examples of other 3-alkylations[1–3] that the reaction does not involve 1-alkylation as part of the reaction sequence.

Experimental[10]

3-Indoleacetic Acid.—A 3-l. stainless steel rocker autoclave was charged with 270 g. (4.1 moles) of 85% potassium hydroxide and 351 g. (3.0 moles) of indole followed by the gradual addition of 360 g. (3.3 moles) of 70% aqueous glycolic acid. The mixture was then heated at 250° under autogenous pressure for 14–22 hr., cooled to 90°, and 1 l. of water added to dissolve the crude potassium indoleacetate. Additional water was added to give a total volume of 3 l. and the solution extracted with ether to remove any neutral material present. The aqueous phase was acidified with concd. hydrochloric acid keeping the temperature 20–30° and finally cooling to 10°. The precipitated product was collected, washed with copious amounts of cold water, and dried. A 90% yield (475 g.) of light cream product was obtained, m.p. 163–165° dec. Crystallization of a sample from water (Darco) gave nearly colorless needles, m.p. 164–166° dec.; reported,[11] m.p. 165°.

Indoleacetamide was prepared *via* the acid chloride by the method of Shaw and Woolley[12] and obtained as colorless needles after crystallization from water, m.p. 149–150°; reported[13] m.p. 150–151°.

Methylated Indoleacetic Acids. General Procedure.—For these preparations (Table I), 75- and 300-ml. stainless steel autoclaves were used in a Magne-Dash apparatus.[14] The reactions were conducted as described for the preparation of indoleacetic acid, except that, in cases where the quantity of starting indole was limited (5–10 g.), water was added in a quantity sufficient to give a level above the dash mechanism. Some of the indole always sublimed into the dash mechanism thereby resulting in decreased yields.

Reaction of Indole with Potassium 2-Hydroxy-3-ethylpentanoate.—In the manner described for the preparation of indoleacetic acid, 100 g. (0.85 mole) of indole, 75 g. (1.14 moles) of 85% potassium hydroxide, and 146 g. (1.0 mole) of 2-hydroxy-3-ethylpentanoic acid[15] were heated at 260° for 20 hr. The crude reaction mixture contained a considerable quantity of a neutral oil which was removed by extraction with ether. Acidification of the aqueous phase gave 22 g. (9.5%) of a red sticky solid. Several crystallizations from cyclohexane afforded pure (2-3′-indolyl)-3-ethylpentanoic acid as slightly reddish needles, m.p. 131–133°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.68; H, 7.59; N, 5.77.

Distillation of the ether extracts afforded 20 g. (20%) of indole, b.p. 118° (1.0 mm.), and 60 g. of a fraction, b.p. 136–150° (1.0 mm.), n^{30}_{D} 1.5563–1.5570. Redistillation afforded 36 g. of nearly colorless 1-(3′-indolyl)-2-ethylbutane; a center fraction boiled at 124° (0.12 mm.), n^{30}_{D} 1.5553. The infrared spectrum of this material was identical to the spectrum of an authentic sample as prepared below.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.83; H, 9.33; N, 6.79.

1-(3′-Indolyl)-2-ethylbutane.—A mixture of 60 g. (0.51 mole) of indole, 20 g. of 85% potassium hydroxide, and 500 ml. of 2-ethylbutanol was charged to a 3-l. stainless steel rocking autoclave and heated at 260° for 21 hr. The reactor was cooled and the contents washed out with ether. After washing the ether solution several times with water, it was distilled yielding 89 g. (87%) of product, b.p. 132–136° (0.6 mm.), n^{30}_{D} 1.5513. A sample was redistilled, b.p. 161° (3.0 mm.), n^{30}_{D} 1.5525, for examination of its infrared spectrum.

Acknowledgment.—The authors are grateful to C. R. McClure for capable assistance and to Q. Quick and his associates for microanalyses and spectral data.

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[10] Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded by a Perkin-Elmer, Model 21, spectrophotometer.

[11] A. Ellinger, *Ber.*, **37**, 1801 (1904).

[12] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

[13] R. Majima and T. Hoshino, *Ber.*, **58**, 2046 (1925).

[14] Autoclave Engineers, Erie, Pa.

[15] Geneoursly supplied by R. W. Kiefer of this laboratory.

Cotton Effects of α,β-Unsaturated Carboxylic Acids[1]

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Received December 26, 1962

Several α,β-unsaturated carboxylic acids show anomalous rotatory dispersion and circular dichroism at relatively long wave lengths (∼250–270 mμ). This finding necessitates the assumption that hitherto undetected very weak bands exist in the absorption spectra of these compounds; one such band is actually observed in the vapor spectrum of β,β-dimethylacrylic acid. Similar Cotton effects are also given by the sodium salt of one of the acids, and by several α,β-unsaturated lactones. In the case of shikimic acid (I), the expected circular dichroism is found, but the corresponding anomalous rotatory dispersion is completely obscured by background effects.

Recently, the study of rotatory dispersion, which has been applied so successfully to ketonic compounds,[2] has been extended increasingly to substances having other chromophores. As a contribution to this field, we wish here to call attention to Cotton effects occurring at unexpectedly long wave lengths in the rotatory dispersion curves of α,β-unsaturated carboxylic acids having asymmetric carbon atoms adjacent to the chromo-

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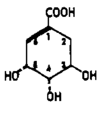
[1] This paper is dedicated to the memory of our friend, Dr. Erich Mosettig.

[2] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.



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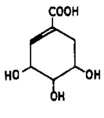

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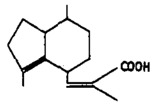

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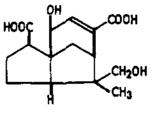

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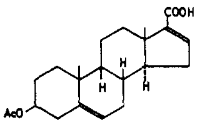

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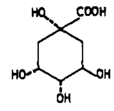

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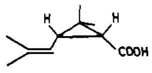

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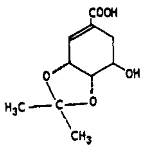

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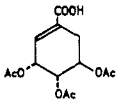

X

phore, and to the existence of weak absorption bands causing these effects. The α,β-unsaturated acids were investigated initially in the hope that it might be possible to reach the Cotton effects produced by the main absorption bands (~210–230 mμ) of the compounds; such effects would be expected to occur below ~240 mμ and hence might still be observable with available instruments (limit ~230 mμ). The substances investigated were: shikimic acid (I), 5-epi-shikimic acid (II),[3] valerenic acid (III),[4] valerenolic acid[4] [(IV), probably a hydroxy derivative of (III)], shellolic acid (V),[5] and 3β-acetoxyetia-5,16-choladienic acid (VI).[6]

All these acids except I (see below) showed anomalous rotatory dispersion (see Fig. 1, 2, and 3). Surprisingly, however, the Cotton effects occurred at much longer wave lengths (λ ~ 250–280 mμ) than had been anticipated; the difference between $\lambda_{\max}$ and first extremum amounts to 40–60 mμ, a fact which makes it very unlikely that the observed effects could be caused by the main absorption bands of the compounds. Where experimentally observable or indicated by extrapolation of the curves obtained, the crossing of the line of zero rotation occurred at ~255–265 mμ. It is thus necessary to assume that the absorption bands responsible for the Cotton effects are located in this spectral region.

More direct experimental evidence for the presence of these postulated bands was obtained by the finding that compounds I–VI (except III, which was not investigated) show circular dichroism in the expected range of wave lengths (244–260 mμ) (see Fig. 1, 2, 3, and 4).

Little attention seems to have been paid to weak absorption bands occurring in the ultraviolet spectra of α,β-unsaturated acids at wave lengths greater than that of the main peak; for instance, the detailed review of these spectra by Nielsen[7] does not mention such bands at all. The literature does, however, contain a few references which may be pertinent: see, *e.g.*, the shoulder at ~250 mμ observed in the spectrum of crotonic acid in water,[8] and the bands above ~250 mμ in the absorption spectra of several substituted acrylic acids in ethanol.[9a]

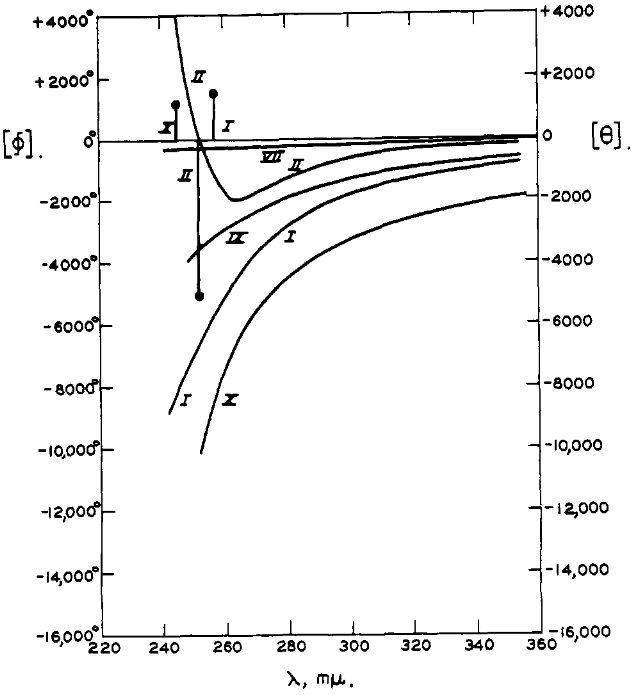

Fig. 1.—Optical rotatory dispersion of: I, water, c = 0.048 (246–240 mμ: c = 0.2); II, water, c = 0.5; VII, water, c = 0.5; IX, ethanol, c = 0.108; X, methanol, c = 0.144. Maxima of circular dichroism indicated by vertical bars; circular dichroism expressed as molecular ellipticities, θ.

In our own work, careful investigation of the solution spectra of I–VI in water or ethanol, and of those of β,β-dimethylacrylic acid, an accessible and readily purified model compound, in water, hexane and cyclohexane failed to indicate the presence of any band in the pertinent region. With dimethylacrylic acid in the gas phase at 70°, however, a weak but distinct band with a maximum at 245 mμ was actually observed, thus giving final proof for the reality of the postulated bands in this area (Fig. 5). Under the same conditions, isovaleric acid, the saturated analog of dimethylacrylic acid, showed only relatively weak end-absorption without any indication of a band.[9b]

Our results thus seem to indicate that weak absorption bands at or above 250 mμ are typical of α,β-unsaturated carboxylic acids; we tentatively ascribe them to $n \rightarrow \pi^*$ transitions of the conjugated carbonyl group, an interpretation which appears to be consistent with their location and low intensity.

The Cotton effects observed in our compounds, and the absorption bands causing them, are definitely connected with the presence of the chromophore C=C—COOH; thus quinic acid (VII), very closely related to II but lacking this chromophore, gives a plain negative

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[3] I. I. Salamon, unpublished work.

[4] G. Büchi, T. L. Popper, and O. Stauffacher, *J. Am. Chem. Soc.*, **82**, 2962 (1960).

[5] P. Yates and G. F. Field, *ibid.*, **82**, 5764 (1960); R. C. Cookson, N. Lewin, and A. Morrison, *Tetrahedron*, **18**, 547 (1962).

[6] A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938).

[7] A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957).

[8] H. Mohler and H. Lohr, *Helv. Chim. Acta*, **21**, 485 (1938); G. O. Burr and E. S. Miller, *Chem. Rev.*, **29**, 419 (1941).

[9] (a) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, **73**, 1564 (1951). (b) NOTE ADDED IN PROOF.—Our sample of β,β-dimethylacrylic acid (recrystallized from hexane and water) was free of impurities detectable by gas-liquid chromatography (diethyleneglycol adipate on Gaschrom P, 131°). Our interpretation of the weak bands around 250 mμ as $n \rightarrow \pi^*$ transitions finds strong support by the proof (W. D. Closson, S. F. Brady, E. M. Kosower, and P. C. Huang, *J. Org. Chem.*, in press) that a weak band (λ ~ 240 mμ) of ethyl acrylate is indeed caused by such a transition. We are indebted to Professor Kosower for a preprint of this paper.

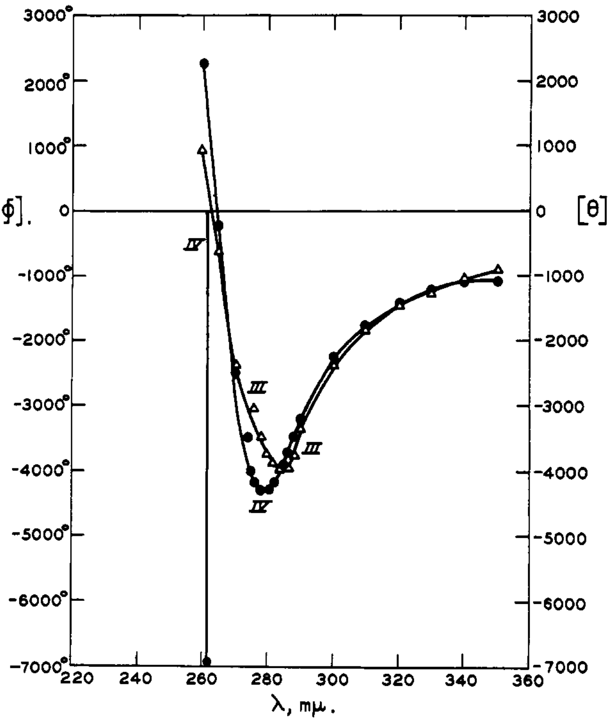

Fig. 2.—Optical rotatory dispersion of: III, methanol, c = 0.1 (270–260 mμ: c = 0.02); IV, methanol, c = 0.1 (272–260 mμ: c = 0.02).

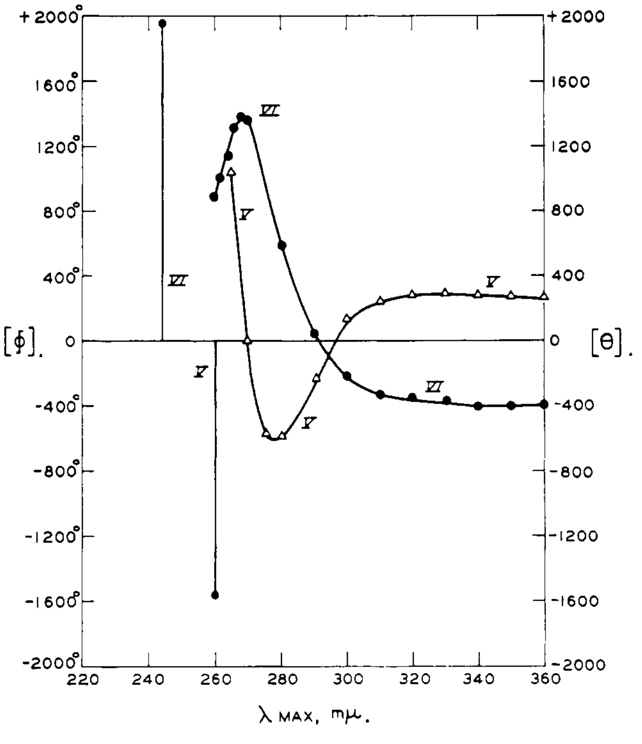

Fig. 3.—Optical rotatory dispersion of: V, methanol, c = 0.115; VI, methanol, c = 0.097.

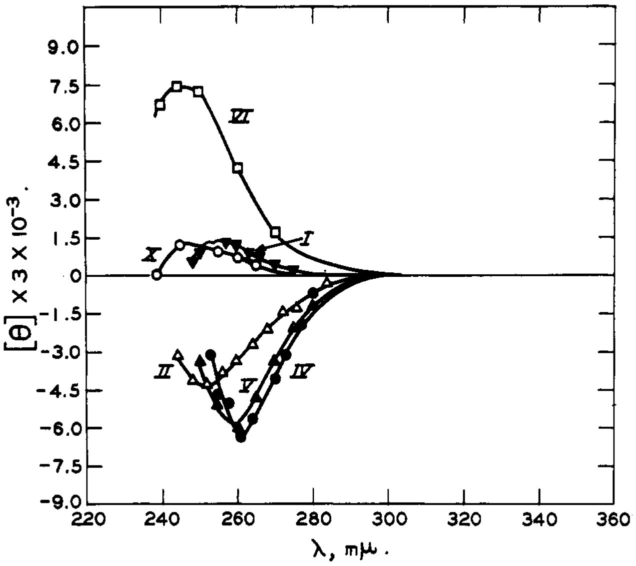

Fig. 4.—Circular dichroism of I, II, IV, V, VI, and X; all in ethanol.

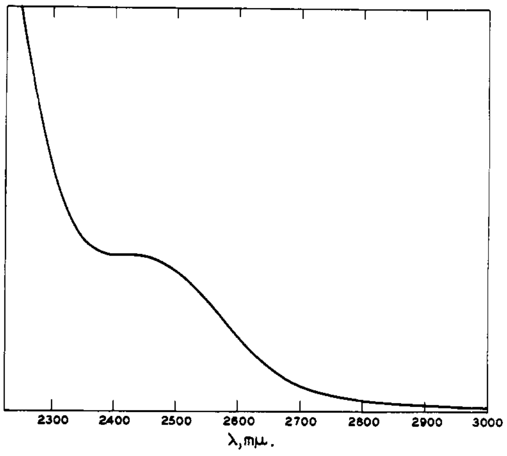

Fig. 5.—Absorption spectrum of β,β-dimethylacrylic acid; vapor at 70°, concentration unknown.

dispersion curve of low intensity without any anomaly down to ~240 mμ (see Fig. 1). Similarly, (+)-*cis*-chrysanthemumcarboxylic acid[10] (VIII) was investigated because it appeared possible that the grouping consisting of carboxyl, cyclopropane ring, and double bond might produce a Cotton effect analogous to the ones found with the α,β-unsaturated acids. Compound VIII, however, gave a smooth curve without anomalies down to 240 mμ, but the high molar rotation values indicate the proximity of a peak at shorter wave lengths ($[\Phi]_{253}$ +5000°; $[\Phi]_{244}$ +8600°, both at c = 0.17; $[\Phi]_{240}$ +14800°, c = 0.034).

Among the α,β-unsaturated acids investigated, I and two of its derivatives, 4,5-isopropylidene-I (IX) and triacetyl-I (X), form an anomalous group. Since II is epimeric with I at the carbon atom which is adjacent to the chromophore, the remainder of the two molecules being identical, one would expect I to show a positive Cotton effect roughly antipodal to the negative one observed for II. Actually, I, IX, and X all give very similar *plain negative* dispersion curves (Fig. 1); no extremum could be reached with any concentration or path length investigated. This anomaly is made even more surprising by the fact that the levorotation of I is much more intense than that of II. It is necessary to ascribe the rotatory dispersion of I, IX, and X to an unusually strong background effect; this interpretation is shown to be correct by the finding that I does give the expected *positive* circular dichroism, antipodal to, but weaker than, the negative one of II (Fig. 1 and 4).

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(10) L. Crombie and M. Elliott, "Progress in the Chemistry of Organic Natural Products," ed. by L. Zechmeister, Springer Verlag, Vienna, Vol. 19, 1961, p. 120, and literature quoted there.

In I, a weak positive Cotton effect thus appears to be completely hidden by an exceptionally large negative background. The reason for this anomaly is not apparent; the similar behavior of I, IX, and X shows that it cannot be ascribed to any simple conformational distortion of the double bond by, *e.g.*, formation of an additional ring through covalent (as in IX) or hydrogen bonds (as in I). In addition to this anomaly of their rotatory dispersions, I and its relatives are also anomalous in showing composite curves of circular dichroism (see Fig. 4), while those of the other acids investigated are simple. These facts indicate that the case of I is a complex one and that attempts at a more detailed interpretation should be postponed until more experimental material is available. It is remarkable, however, that the empirical rule of Bose and Chatterjee[11] correctly predicts that I should have a more negative $[\alpha]_D$ value than II.

The conjugated chromophore of I thus appears to behave entirely normally, but this fact could be detected only by study of the circular dichroism, not by that of optical rotatory dispersion, where the effect of this chromophore is completely obscured by background influences.[12]

The occurrence of Cotton effects in this area is not restricted to the free acids; their salts and esters seem to show the same behavior. Thus the sodium salt of V in aqueous solution gives a rotatory dispersion curve very similar to that of the free acid but shifted to greater negative rotations; though at 273 mμ, [Φ] −1900°. Similarly, several α,β-unsaturated lactones have been found to exhibit extrema in this area; *e.g.*, digitoxigenin, $[\Phi]_{256}$ +4600°, α-levantenolide,[13] $[\Phi]_{266} = +5930°$, and β-levantenolide,[13] $[\Phi]_{266} = -5940°$. The investigation is being extended to other compounds of this type.

It remains to be seen, when additional experimental material becomes available, whether the observation of such rotatory anomalies may be of value for the study of stereochemical problems, and what correlation exists between the direction of these Cotton effects and the configuration of the molecule.

Acknowledgment.—Samples were kindly furnished by Drs. I. I. Salamon (II), G. Büchi (III and IV), P. Yates (V), A. W. Burgstahler (VI), and M. S. Schechter (VIII). Compound I was a sample donated by the late Dr. H. O. L. Fischer; some of the measurements on this compound, and those on VII, were carried out with products from Nutritional Biochemicals Corporation. IX and X were prepared as described by Fischer and Dangschat.[14] The rotatory dispersions were measured with a Rudolph recording spectropolarimeter using a variety of solvents and cell lengths. Circular dichroism measurements were made on the Jouan Dichrograph of the Chemistry Department of the University of Strasbourg. The authors are much indebted to Drs. G. Ourisson and P. Witz, and Miss H. Hermann for these measurements, to Mr. H. K. Miller for use of the spectropolarimeter, to Drs. A. K. Bose, E. Charney, and W. Klyne for stimulating discussions, and to Mr. J. R. Mills for valuable technical assistance.

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[11] A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958).

[12] *Cf.* C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **84**, 4552 (1962).

[13] J. A. Giles and J. N. Schumacher, *Tetrahedron*, **14**, 246 (1961); **18**, 260 (1962).

[14] H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935).

Preparation of *t*-Butyl Esters of Free Amino Acids[1]

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Received December 31, 1962

Most amino acids dissolve in dioxane–sulfuric acid mixtures and react with isobutene to form the *t*-butyl esters in 60–75% yield. The monobenzyl esters of aspartic and glutamic acid form benzyl-*t*-butyl esters, which can be hydrogenated to the mono *t*-butyl esters. β-*t*-Butyl L-aspartate and γ-*t*-butyl L-glutamate gave the N-carboxyanhydrides when treated with phosgene.

The *t*-butyl esters of amino acids are useful carboxyl-protecting groups in peptide synthesis because they are cleaved readily by acids. The esters have been prepared from N-acylated amino acids by reaction with isobutene,[2] or *t*-butyl acetate[3] and by conversion of the α-chloro-*t*-butyl esters to the amino esters *via* the azide,[4] a process which yields racemic esters. Some amino esters have been prepared from the free amino acids by reaction with *t*-butyl acetate and perchloric acid.[5] In a preliminary communication[6] we described a procedure for converting free amino acids to their *t*-butyl esters by reaction with isobutene in a mixture of dioxane and sulfuric acid. The yields reported at that time were around 45%. By using a more dilute reaction mixture, we have been able to raise the yields to 60–75% in many cases. The yield depends on the solubility of the amino acid in dioxane–sulfuric acid; L-phenylalanine is quite soluble and is converted rapidly to its *t*-butyl ester in 75% yield, while glycine is only slightly soluble and forms little ester. Diethylene glycol–sulfuric acid is also a satisfactory solvent for the reaction.

The four benzyl-*t*-butyl diesters of L-aspartic and L-glutamic acid were prepared from the monobenzyl esters. Hydrogenation of these provided the four

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[1] This work was begun at the Lilly Research Laboratories, Indianapolis, and continued at the present address, supported in part by a research grant from the U. S. Public Health Service (GM-K3-17960). Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill. September, 1961.

[2] G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

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